ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2020, **7**, 3434

Visible-light-mediated Barbier allylation of aldehydes and ketones *via* dual titanium and photoredox catalysis†

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Received 6th February 2020,
Accepted 4th September 2020

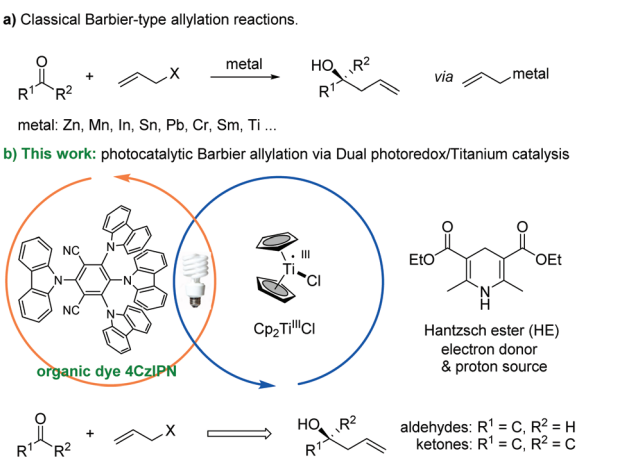
DOI: 10.1039/d0qo00171f

rsc.li/frontiers-organic

This study reports a photocatalytic Barbier-type allylation of various aldehydes and ketones with allyl halides for the synthesis of homoallylic alcohols driven by dual titanium and photoredox catalysis. This environmentally benign process uses the organic dye 2,4,5,6-(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) as a photocatalyst and Hantzsch ester (HE) as an electron donor instead of stoichiometric metallic reductants.

Homoallylic alcohols and their derivatives are important building blocks for the synthesis of various biologically active natural products and pharmaceuticals.[1,2] Barbier-type allylation reactions are important methods for the synthesis of homoallylic alcohols.[3,4] Due to their versatility and large number of applications in organic synthesis, different transition metals, including Zn, Mn, In, Sn, Pb, Cr, Sm, and Ti, have been used in the Barbier-type allylation strategy (Scheme 1a).[5–9] Among them, titanium (Ti), the seventh most abundant metal on Earth, has attracted considerable attention due to its general non-toxicity and environmental friendliness.[10–14] However, the regeneration of sensitive allyltitanium reagents that require superstoichiometric metallic reductants (Zn or Mn) and large quantities of additives (Me_3SiCl and 2,4,6-collidine) is undesirable in terms of the development of environmentally benign processes and has restricted their widespread application. As a consequence, it is highly desirable to find a new and greener catalytic system for practical applications. In recent years, metallaphotoredox catalysis has become a powerful approach in organic synthesis.[15–22] This approach expands the synthetic utility of visible light in modern organic synthesis and has successfully led to the discovery of numerous novel reaction modes under eco-friendly conditions.[23,24] We recently reported a dual photoredox and titanium catalysis for the reductive opening\cyclization of epoxides.[22a–c] In order to develop this dual catalysis further, we wondered whether it could also be used in the Barbier-type allylation of carbonyl compounds with allyl halides, meanwhile overcoming the aforementioned limitations (Scheme 1b). During the revision of the manuscript, a similar study of allylation with aldehydes was reported.[22f]

We chose 4-anisaldehyde **1a** and allyl bromide as model substrates for the optimization of the reaction conditions (Table 1). After a systematic variation of different reaction parameters, we successfully identified the optimal reaction conditions under which a mixture of Cp_2TiCl_2 (5.0 mol%), the low-cost and readily available organic dye 4CzIPN (1.0 mol%, $E_{1/2}^{P/P-}$ = −1.21 V *vs.* SCE in acetonitrile), HE (2.0 equiv.) and allyl bromide (2.0 equiv.) in tetrahydrofuran (THF) at room temperature with irradiation by a 450 nm light emitting diode (LED) lamp for 12 hours gave the desired product **2a** in excel-



Scheme 1 (a) Traditional Barbier-type allylation reactions. (b) Dual titanium and photoredox catalysis enabled allylation of carbonyl compounds.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/d0qo00171f

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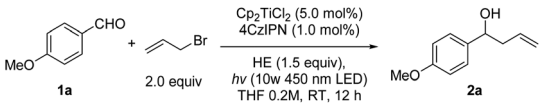
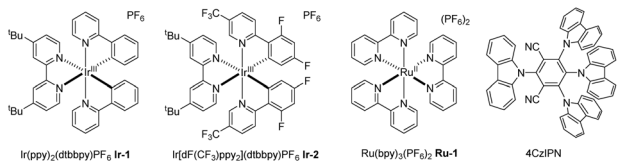
Table 1 Optimization of the reaction conditions[a,b]



Entry	Variation from standard conditions	Yield (%)
1	None	92
2	**Ir-1** instead of 4CzIPN	65
3	**Ir-2** instead of 4CzIPN	86
4	**Ru-1** instead of 4CzIPN	0
5	Dichloroethane instead of THF	32
6	*N,N*-Dimethylformamide instead of THF	24
7	0.05 M instead of 0.2 M	63
8	0.4 M instead of 0.2 M	69
9	2 h instead of 12 h	85
10	4 h instead of 12 h	92
11	DIPEA instead of HE	0
12	No titanocene	<5
13	No HE	0
14	No photocatalyst	0
15	No *hv*	0

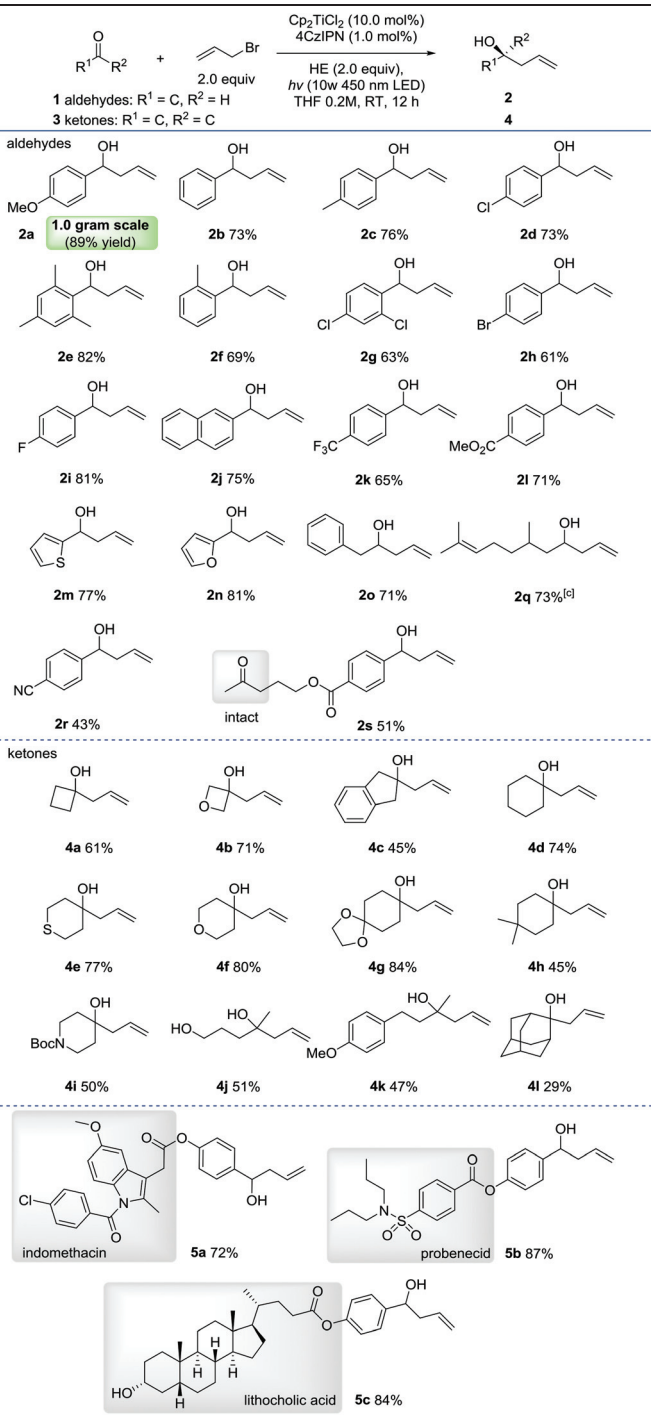
[a] Reaction conditions: **1a** (1.0 mmol scale). [b] Yields were determined by ^{1}H NMR spectroscopy *versus* an internal standard.



lent 92% yield (entry 1). It is worth noting that no extra additives were required for the reaction. Further screening of other photocatalysts revealed that $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**Ir-2**, 1.0 mol%, $E_{1/2}^{IV/III*} = -0.96$ V *vs.* SCE in acetonitrile) is a suitable alternative, which led to complete conversion with an 86% yield (entry 3). Various solvents, including dichloroethane and *N,N*-dimethylformamide, were evaluated, and they all resulted in less yield (entries 5 and 6). Decreasing or increasing the reaction concentration decreased the yields (entries 7 and 8). Actually, the reaction proceeded quite fast and gave 85% yield after only 2 hours (entries 9 and 10). The use of other organic electron donors, such as *N,N*-diisopropylethylamine (DIPEA), instead of HE, gave no product (entry 11). Additionally, the reaction did not proceed in the absence of Cp_2TiCl_2, HE, the photocatalyst, or visible light (entries 12–15).

After establishing the optimal reaction conditions, we investigated the scope of the allylation reaction. Certainly, the reaction worked well with various aldehydes and ketones affording homoallylic alcohols in generally good to excellent yields (Table 2). The reaction system was not sensitive to the substituent effect of the aromatic ring. Both electron rich groups, such as methoxyl **2a**, and electron withdrawing groups, such as fluorine **2i**, trifluoromethyl **2k**, and ester **2l**, gave the alcohols in satisfactory yields. The sterically hindered mesitylaldehyde **2e** and adamantanone **4l** were also successfully allylated. Heteroatoms, such as oxygen **4b** and sulfur **4e** and protected amine **4i**, did not interfere with the catalytic cycle. Moreover,

Table 2 Scope of aldehydes and ketones[a,b]



[a] Reaction conditions: **1** and **3** (1.0 mmol scale). [b] Yields were determined by ^{1}H NMR spectroscopy *versus* an internal standard. [c] 3.0 mol% **Ir-2** was used.

various heteroarenes, the most widely used core structures in pharmaceutical synthesis, including furan **2n** and thiophene **2m**, were also compatible with this dual catalysis. Photocatalytic conditions offered broad compatibility with numerous synthetically important and sensitive functional

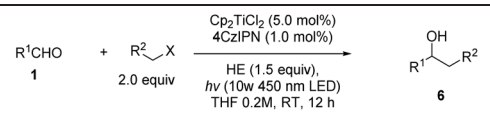
groups due to the extremely mild conditions. These included free alcohol **4j**, ether **4f**, alkene **2q**, ester **2l** and bromobenzene **2h**. Notably, **2s** was obtained in good yield without addition to ketone. This finding clearly indicated that our approach has good chemoselectivity and can discriminate between aldehydes and ketones. To demonstrate the potential applicability of this dual catalysis strategy in late-stage functionalization, indomethacin, lithocholic acid, and probenecid derivatives were used, and the desired products **5a–5c** were obtained in good yields. To determine the scalability of the reaction, the gram-scale synthesis of **2a** was performed under standard conditions. Satisfyingly, product **2a** was obtained without deterioration in the good 89% yield. The low cost of 4CzIPN, nontoxic titanium, broad compatibility with sensitive functional groups, and operationally simple conditions are appealing for laboratory and industrial applications.

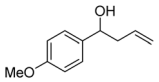
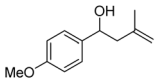
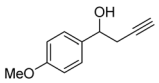
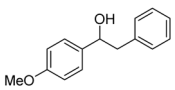
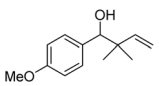
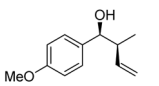
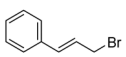
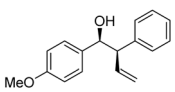
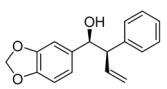
To further assess the generality of the currently developed dual photoredox and titanium catalytic system, a series of analogous Barbier-type reactions were also tested. Similarly, good results were obtained, as shown in Table 3. Allyl chloride and 3-chloro-2-methylpropene were used as substrates for the allylation and they gave **6a** and **6b**, respectively, in good yields (entries 1 and 2). Both propargylation and benzylation are useful C–C bond-forming reactions in organic synthesis. The treatment of aldehyde **1a** with propargyl halides and benzyl halides produced alcohols **6c** and **6d** in moderate yields (entries 3–6). In order to study the regio- and stereoselectivities of the reaction, we also examined the behaviour of more allylic bromides. To this end, 3,3-dimethylallyl bromide, 3-chloro-1-butene, and cinnamyl bromide were used as substrates to perform the reaction (entries 7–9). In all reactions, good regioselectivity was achieved in favour of the branched products **6e–6f**.[25] These results suggest that the ketyl radical intermediates are not likely involved in the allylation process. Remarkably, a high level of stereoselectivity was achieved for products **6f–6h**.

We also conducted Stern–Volmer luminescence quenching studies to gain further insight into the nature of the photocatalytic process and the mechanism of the reaction (see ESI S2†). These studies showed that HE and Cp_2TiCl_2 can quench the excited state photocatalyst. Interestingly, allyl bromide also quenched the luminescence of 4CzIPN with a rate of 5.82×10^8 L M^{-1} s^{-1}. This result indicated that allyl bromide can be reduced by photoexcited 4CzIPN and allyl radicals could be produced. Furthermore, the quantum yield of the reaction was calculated to be 0.016, and thus the radical-chain mechanism is unlikely (see ESI S4†).

Based on these results and previous reports in the literature,[5–7] we tentatively propose the following catalytic cycle (Fig. 1). First, Cp_2TiCl_2 is reduced to $Cp_2Ti^{III}Cl$ by a photoexcited 4CzIPN. The strong oxidant $4CzIPN^+$ species is then reduced by HE to produce HE^+, which can further participate in electron transfer events and ultimately produce **pyH$^+$**. The allyl bromide would be reduced by photoexcited 4CzIPN* to yield an allyl radical **7**. Alternatively, **7** can also be produced *via* the reaction of allyl bromide with $Cp_2Ti^{III}Cl$. The resulting **7** can react with $Cp_2Ti^{III}Cl$ and yield nucleophilic allyltitanium

Table 3 Scope of alkyl halides[a,b]



Entry	Alkyl halides	Products	Yields
1		 **6a**	84%
2		 **6b**	52%
3		 **6c**	86%
4			47%
5		 **6d**	76%
6			50%
7		 **6e**	86%
8		 **6f**	58%, dr = 10 : 1[c]
9		 **6g**	83%, dr = 10 : 1[c]
		 **6h**	72%, dr > 20 : 1[c]

[a] Reaction conditions: **1a** (1.0 mmol scale). [b] Yields were determined by ^{1}H NMR spectroscopy *versus* an internal standard. [c] Diastereomeric ratios were determined by ^{1}H NMR spectroscopy.

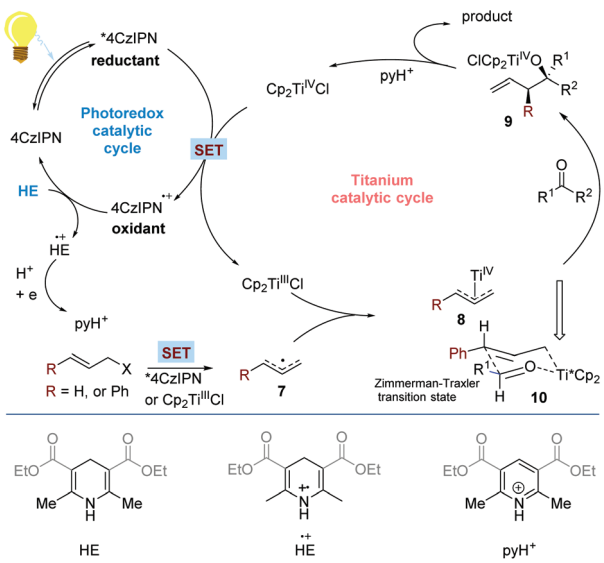


Fig. 1 Proposed catalytic mechanism.

species **8**. The coupling of the allyltitanium complex **8** with the carbonyl group would form a new C–C bond in the alkoxytitanium product **9**. The protonation of the Ti–oxygen bond by pyH^+, which acts as a proton source, releases Ti^{IV} and the homoallylic alcohol product. Eventually, 4CzIPN can regenerate $Cp_2Ti^{III}Cl$ for the next catalytic cycle. The *anti*-selectivity of homoallylic alcohols **6f–6h** (Table 3) can be explained by the Zimmerman–Traxler transition state **10** in which the oxygen of the aldehyde coordinates to the titanium. The R group of the aldehyde and the phenyl group preferentially adopt an equatorial disposition, leading to the formation of an *anti* isomer.

Conclusions

In summary, this study reports a photocatalytic Barbier-type allylation reaction driven by a dual catalytic system consisting of nontoxic titanium and the organic dye 4CzIPN. This eco-friendly photoredox process used a Hantzsch ester as both an electron donor and a proton donor. Thus, super-stoichiometric metals and external additives are no longer required. This operationally simple, scalable, and efficient method provides an efficient approach for the synthesis of valuable homo-allylic alcohols in good yields. The generality of this method is also demonstrated through propargylation, benzylation and prenylation reactions. The development of new transformations based on dual photoredox and titanium catalysis is currently under way in our lab.

Experimental section

To a solution of **1a** (1.0 mmol, 1.0 eq.), HE (2.0 mmol, 2.0 eq.), Cp_2TiCl_2 (10.0% mol), and 4CzIPN (1.0% mol) in THF was added allyl bromide (2.0 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature using a 10 W 450 nm LED for 12 h. The ^1H NMR analysis of the crude product was performed using 1,3,5-trimethyoxybenzene as the internal standard and it was purified by column chromatography.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from the Fundamental Research Funds for the Central Universities (No. DUT19LK31). We thank WATTCAS CHEM-TECH Co., Ltd for kindly providing the photoreactor.

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